Peripheral arterial disease (PAD) is a distinct clinical manifestation of atherosclerosis, with an associated long-term risk of coronary and cerebrovascular events that is equivalent to that of a primary diagnosis of myocardial infarction or ischemic stroke. The prevalence of PAD, as estimated by an abnormal ankle-to-brachial systolic pressure index (ABI <0.9), is closely linked to age, afflicting up to 20% or more of individuals >55 years of age in Western societies. The majority of patients with PAD are asymptomatic, but recognition of the disease is clinically important because it may be the primary manifestation of systemic atherosclerosis. Indeed, numerous studies have demonstrated a correlation between the global risk of cardiovascular events and ABI, which portends a more dire outcome for those with increasing degrees of hemodynamic compromise in the limb. The major risk factors for PAD, aside from age, are cigarette smoking, diabetes mellitus, dyslipidemia, hyperhomocysteinemia, and hypertension. Among these, the recent explosion in the worldwide prevalence of diabetes mellitus is of particular concern, particularly because the risk of both mortality and limb loss in diabetic PAD patients is increased several-fold. Thus, a major focus of clinical management in PAD is on secondary prevention, including the aggressive treatment of these risk factors by dietary and behavioral modification, combined with medical therapies. Present evidence suggests that PAD patients should receive lifelong antiplatelet therapy, treatment with a hydroxymethylglutaryl coenzyme A reductase inhibitor (statin), and appropriate antihypertensive therapy, which should probably include an angiotensin-converting enzyme inhibitor.

Symptomatic PAD, which affects approximately one third of all PAD patients, is most commonly manifested as intermittent claudication (IC), a walking impairment that results at least in part from a classic mismatch between blood supply and metabolic demand of the leg muscle groups. Critical limb ischemia, the most severe form of PAD, is defined by the presence of ischemic rest pain, ulceration, or gangrene of the affected extremity. It occurs in fewer than 5% to 10% of PAD patients but portends a markedly worse prognosis for both life and limb. Patients with IC have a generally more benign course with respect to the limb, and the disease is most commonly slowly progressive. In a 5-year period, ≈5% of patients with IC will undergo major amputation, whereas 20% to 30% may have significant progression of symptoms. PAD patients also have a high preponderance of atypical leg symptoms that are associated with reduced functional capacity and impaired quality of life. In this regard, the high frequency of associated comorbidities, including arthritic conditions, neurological impairments, and cardiopulmonary disorders, adds significant complexity to the diagnosis and management of walking impairment in the PAD population. Indeed, it is well recognized that the severity of disability in IC, as reported by the patient, is not predictably linked to objective hemodynamic measures such as ABI. This makes for a significant possibility of both reporting bias and placebo effects in clinical trials evaluating therapies designed to improve functional performance in IC. Objective measurements, such as exercise treadmill testing using standardized protocols, are thus considered the “gold standard” for assessing meaningful effects in clinical trials.

Revascularization of the limb, including either open surgical or endovascular approaches, can provide dramatic symptomatic relief in IC; however, the morbidity, mortality, and mid-term failure rates of these interventions are not insignificant, and thus, the use of noninvasive treatments (eg, exercise, medical therapies) is attractive. Particularly attractive would be a drug profile of high safety, patient tolerance, and clear benefits in terms of both cardiovascular risk reduction and limb outcomes. Presently, both antiplatelet drugs and statins appear to meet these broad goals, with statins also having a potential benefit with regard to IC symptoms.

There is clearly a need for better medical therapies in this area, as reflected by the continued interest of the pharmaceutical industry. In the United States, pentoxifylline and cilostazol are the only 2 drugs specifically approved for the treatment of IC. Many other agents with vasodilatory, hemorheologic, antithrombotic, chelating, and metabolic properties have been examined, with limited evidence to support their clinical application. Among these is buflomedil, an α1- and α2-adrenoconstrictive agent that is approved for use in Europe and has been under evaluation for more than 2 decades. In the present issue of Circulation, Leizorovicz and colleagues report on the results of the LIMB (Limbs International Medicinal Buflomedil) study, a large, multicenter, randomized clinical trial that demonstrates the challenges of randomized controlled trial design and interpretation in this population.
The LIMB study was designed as a double-blind, placebo-controlled, randomized controlled trial evaluating the safety and efficacy of buflomedil in patients with IC and documented PAD who had an ABI between 0.3 and 0.8 (to meet eligibility requirements). A total of 2078 patients were randomized at 1 of 133 participating European centers. All patients were followed up for at least 24 months, with the median duration being 2.75 years. The primary efficacy outcome was defined as a composite of cardiovascular events, which included cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and "symptomatic deterioration" of PAD. This latter category was defined by the authors as including "invalidating claudication," ischemic rest pain, ulceration or gangrene, blue toe, and "acute or subacute ischemia" that required either intravenous treatment, rehabilitation in a specialized center, surgery, angioplasty, or leg amputation. The symptomatic deterioration end point was to have been corroborated by hemodynamic or imaging assessments. All critical cardiovascular and safety events were reviewed by an independent critical events committee in a blinded fashion. Pain-free and maximal walking distances were assessed by patient questioning, not by treadmill exercise testing. The study was powered with the assumptions of a 20% to 24% incidence of critical cardiovascular events in the placebo group and a 25% risk reduction associated with active therapy, with $\beta$ set to 0.9 and $\alpha$ set at 0.05. A semiblinded interim analysis was conducted after the 1000th patient, which is said to have confirmed the statistical hypotheses.

The authors report that the overall rate of critical events, as defined above, was significantly lower in the buflomedil group (9.1% versus 12.4%, $P=0.0163$), and this effect remained significant even with adjustment for critical covariates such as age, diabetes mellitus, and baseline ABI. On the surface, this roughly 25% risk reduction would appear to be clinically meaningful; however, a closer look at the data leads one to a much more conservative interpretation of the findings.

First, the overall rate of cardiovascular events was much less than anticipated, on the order of 10%. The "hard" end points of all-cause mortality, cardiovascular death, myocardial infarction, stroke, and amputation were equivalent between the treatment groups. The difference in the primary trial end point, to a large degree, is dependent on the outcome of "symptomatic deterioration of PAD," of which several components are "soft." Few would argue with a documented deterioration to critical limb ischemia or the occurrence of surgery or angioplasty as trial end points (although for many claudicants, the choice of intervention may simply reflect a degree of frustration with conservative therapy, as opposed to worsening PAD). However, the development of "invalidating claudication," need for intravenous treatments, or referral to a specialized rehabilitation setting are more nebulous end points and are not clearly related to progression of disease (supporting objective evidence was not given). They are also difficult to interpret for practitioners in the United States, who do not commonly use either intravenous treatments or specialized rehabilitation settings for IC. The authors compare the magnitude of risk reduction for buflomedil to that observed for antiplatelet agents, statins, and angiotensin-converting enzyme inhibitors in PAD patients, which is a bit disingenuous in that the critical evidence for these drugs is based on hard cardiovascular end points. In addition, only $\approx$15% of the LIMB study population was diabetic, and only 15% to 17% of patients were taking statin drugs concomitantly; both of these features limit the generalizability of the findings.

What, then, can we say about the effects of buflomedil on IC symptoms and the limb per se? Unfortunately, as already noted, the LIMB study did not use treadmill testing as objective evidence of symptomatic improvement. The self-reported data suggest that patients who were assigned to active treatment did in fact experience a functional benefit. A statistically significant improvement in ABI was noted, but the clinical significance of a 9.2% relative change (ie, <0.1 absolute change in the ABI value) is quite unclear. The findings are only suggestive and must be taken in the context of the prior literature. Two Cochrane reviews, including an updated meta-analysis in 2007, have found little evidence to support the efficacy of buflomedil for IC.18,19 A third, older meta-analysis had concluded there was evidence for a positive effect in at least 60% of patients.20 Until an adequately powered randomized controlled trial is conducted with an objective measurement (treadmill test), the question of whether buflomedil significantly improves walking performance in IC patients remains unanswered.

The PAD population of patients is a challenge for clinical trials because of their advanced age, prevalent comorbidities, and functional impairments. The LIMB study investigators are to be congratulated for executing this large randomized controlled trial with minimal loss to follow-up over several years. Unfortunately, the compromises made in study design and the equivalent findings with respect to hard cardiovascular end points severely limit the importance of this trial for vascular specialists. The clinical evidence to date does not support the inclusion of buflomedil among the few pharmacological agents that provide meaningful benefit for PAD patients.

Disclosures

None.

References


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